

BREAKING ADVANCES

- 2493** Highlights from Recent Cancer Literature

CANCER RESEARCH 75th ANNIVERSARY COMMENTARIES

- 2495** The Impact of Nathan Mantel's "The Detection of Disease Clustering and a Generalized Regression Approach"
Michelle Wynn, Kelley M. Kidwell, and Sofia D. Merajver
- 2497** PDT: What's Past Is Prologue
Keith A. Cengel, Charles B. Simone II, and Eli Glatstein

REVIEWS

- 2500** Mitochondrial Sirtuins in Cancer: Emerging Roles and Therapeutic Potential
Jasmine George and Nihal Ahmad
- 2507** Carcinoma Cell Hyaluronan as a "Portable" Cancerized Prometastatic Microenvironment
Eva A. Turley, David K. Wood, and James B. McCarthy

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 2513** Elucidation of the Roles of Tumor Integrin $\beta 1$ in the Extravasation Stage of the Metastasis Cascade
Michelle B. Chen, John M. Lamar, Ran Li, Richard O. Hynes, and Roger D. Kamm
- Précis:* High spatio-temporal resolution imaging in a novel model of the tumor microenvironment reveals the precise cellular events through which integrin $\beta 1$ promotes extravasation of tumor cells from the vasculature during the final stage of the metastatic cascade.

MICROENVIRONMENT AND IMMUNOLOGY

- 2525** TGF β Signaling in the Pancreatic Tumor Microenvironment Promotes Fibrosis and Immune Evasion to Facilitate Tumorigenesis
Daniel R. Principe, Brian DeCant, Emman Mascariñas, Elizabeth A. Wayne, Andrew M. Diaz, Naomi Akagi, Rosa Hwang, Boris Pasche, David W. Dawson, Deyu Fang, David J. Bentrem, Hidayatullah G. Munshi, Barbara Jung, and Paul J. Grippo
- Précis:* Targeting the tumor-promoting effects of stromal-derived TGF β signaling in pancreatic cancer may constitute an applicable strategy in patients no longer benefiting from TGF β -induced tumor suppression.

- 2540** Feasibility of Telomerase-Specific Adoptive T-cell Therapy for B-cell Chronic Lymphocytic Leukemia and Solid Malignancies



Sara Sandri, Sara Bobisse, Kelly Moxley, Alessia Lamolinara, Francesco De Sanctis, Federico Boschi, Andrea Sbarbati, Giulio Fracasso, Giovanna Ferrarini, Rudi W. Hendriks, Chiara Cavallini, Maria Teresa Scupoli, Silvia Sartoris, Manuela Iezzi, Michael I. Nishimura, Vincenzo Bronte, and Stefano Ugel

Précis: This study exploited the tumor-specific expression of human telomerase to generate a high avidity T-cell receptor for adoptive cell therapy of a B-cell leukemia, illustrating its potency and safety in a preclinical model.

- 2552** CSF1 Overexpression Promotes High-Grade Glioma Formation without Impacting the Polarization Status of Glioma-Associated Microglia and Macrophages

Ishani De, Megan D. Steffen, Paul A. Clark, Clayton J. Patros, Emily Sokn, Stephanie M. Bishop, Suzanne Litscher, Vilena I. Maklakova, John S. Kuo, Fausto J. Rodriguez, and Lara S. Collier

Précis: CSF1 mediates oncogenic effects during gliomagenesis by acting in the tumor microenvironment, but its actions do not appear to be mediated by altering the polarization state of glioma-associated macrophages/microglia as expected.

- 2561** IL15 Agonists Overcome the Immunosuppressive Effects of MEK Inhibitors

Michael J. Allegranza, Melanie R. Rutkowski, Tom L. Stephen, Nikolaos Svoronos, Amelia J. Tesone, Alfredo Perales-Puchalt, Jenny M. Nguyen, Fahmida Sarmin, Mee R. Sheen, Emily K. Jeng, Julia Tchou, Hing C. Wong, Steven N. Fiering, and Jose R. Conejo-Garcia

Précis: Small molecules used as anticancer-targeted therapies have significant immunosuppressive effects by interfering with signaling pathways that are critical for T-cell responses, but in cases of MEK inhibitors, these effects can be effectively rescued by IL15 superagonists available for clinical administration.

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2573 Stromal-Based Signatures for the Classification of Gastric Cancer

Mark T. Uhlik, JIangang Liu, Beverly L. Falcon, Seema Iyer, Julie Stewart, Hilal Celikkaya, Marguerita O'Mahony, Christopher Sevinsky, Christina Lowes, Lary Douglass, Cynthia Jeffries, Diane Bodenmiller, Sudhakar Chintharlapalli, Anthony Fischl, Damien Gerald, Qi Xue, Jee-yun Lee, Alberto Santamaria-Pang, Yousef Al-Kofahi, Yunxia Sui, Keyur Desai, Thompson Doman, Amit Aggarwal, Julia H. Carter, Bronislaw Pytowski, Shou-ching Jaminet, Fiona Ginty, Aejaz Nasir, Janice A. Nagy, Harold F. Dvorak, and Laura E. Benjamin

Précis: Classifying gastric cancer based on stromal gene expression signatures highlights a new approach to identify putative biomarkers to predict patient responses to antiangiogenesis agents and immunotherapy.

MOLECULAR AND CELLULAR PATHOBIOLOGY

2587 The Prosurvival IKK-Related Kinase IKKε Integrates LPS and IL17A Signaling Cascades to Promote Wnt-Dependent Tumor Development in the Intestine

Serkan Ismail Göktuna, Kateryna Shostak, Tieu-Lan Chau, Lukas C. Heukamp, Benoit Henny, Hong-Quan Duong, Aurélie Ladang, Pierre Close, Iva Klevernic, Fabrice Olivier, Alexandra Florin, Grégory Ehx, Frédéric Baron, Maud Vandereyken, Souad Rahmouni, Lars Vereecke, Geert van Loo, Reinhard Büttner, Florian R. Greten, and Alain Chariot

Précis: Wnt-driven intestinal tumors initially developing in the absence of inflammatory cues appear to trigger prosurvival signaling cascades that also promote the establishment of a proinflammatory environment supportive of tumor growth.

2600 Synergistic Activation of ERα by Estrogen and Prolactin in Breast Cancer Cells Requires Tyrosyl Phosphorylation of PAK1

Peter Oladimeji, Rebekah Skerl, Courtney Rusch, and Maria Diakonova

Précis: These findings illustrate a mechanism of drug resistance in breast cancer and reveals a potential strategy to improve therapeutic responses.

2612 Genomic Loss of *DUSP4* Contributes to the Progression of Intraepithelial Neoplasm of Pancreas to Invasive Carcinoma

Naoki Hijiya, Yoshiyuki Tsukamoto, Chisato Nakada, Lam Tung Nguyen, Tomoki Kai, Keiko Matsuura, Kohei Shibata, Masafumi Inomata, Tomohisa Uchida, Akinori Tokunaga, Kohei Amada, Kuniaki Shirao, Yasunari Yamada, Hiromu Mori, Ichiro Takeuchi, Masao Seto, Masahiro Aoki, Mutsuhiro Takekawa, and Masatsugu Moriyama

Précis: Loss of chromosome 8p occurring early in development of pancreatic cancer can be compensated for therapeutic inhibition of ERK signaling, a potentially useful strategy to prevent the progression of invasive disease.

2626 The Ribonucleic Complex HuR-MALAT1 Represses CD133 Expression and Suppresses Epithelial-Mesenchymal Transition in Breast Cancer

Elisa Latorre, Stephana Carelli, Ivan Raimondi, Vito D'Agostino, Iliaria Castiglioni, Chiara Zucal, Giacomina Moro, Andrea Luciani, Giorgio Ghilardi, Eleonora Monti, Alberto Inga, Anna Maria Di Giulio, Alfredo Gorio, and Alessandro Provenzani

Précis: The mechanism underlying derepression of a critical metastasis-inducing gene in breast cancer appears to involve a regulatory complex that requires the presence of a long noncoding RNA component to suppress EMT-like traits.

2637 An Epigenetic Reprogramming Strategy to Resensitize Radioresistant Prostate Cancer Cells

Claudia Peitzsch, Monica Cojoc, Linda Hein, Ina Kurth, Katrin Mäbert, Franziska Trautmann, Barbara Klink, Evelin Schröck, Manfred P. Wirth, Mechthild Krause, Eduard A. Stakhovskiy, Gennady D. Telegeev, Vladimir Novotny, Marieta Toma, Michael Muders, Gustavo B. Baretton, Fiona M. Frame, Norman J. Maitland, Michael Baumann, and Anna Dubrovskaya

Précis: A preclinical rationale for the investigation of therapeutic strategies combining radiation and epigenetic agents for the treatment of prostate cancer is presented by findings that prostate cancer cells can be forced to respond to therapy by pharmacological rewiring of the epigenome.

2652 Measurement of Endogenous versus Exogenous Formaldehyde-Induced DNA-Protein Crosslinks in Animal Tissues by Stable Isotope Labeling and Ultrasensitive Mass Spectrometry

Yongquan Lai, Rui Yu, Hadley J. Hartwell, Benjamin C. Moeller, Wanda M. Bodnar, and James A. Swenberger

Précis: This study describes a mass spectrometry-based method that can readily define the distribution of DNA-protein crosslinks in various tissues, with implications for cancer risk assessment.




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- 2662** Rab11-FIP1C Is a Critical Negative Regulator in ErbB2-Mediated Mammary Tumor Progression
Pierre-Luc Boulay, Louise Mitchell, Jason Turpin, Julie-milie Huot-Marchand, Cynthia Lavoie, Virginie Sanguin-Gendreau, Laura Jones, Shreya Mitra, Julie M. Livingstone, Shirley Campbell, Michael Hallett, Gordon B. Mills, Morag Park, Lewis Chodosh, Douglas Strathdee, Jim C. Norman, and William J. Muller
Précis: An effector of small GTPase Rab11 functions as a tumor suppressor in ErbB2-amplified breast cancer, but as an oncogene in other breast tumor subtypes, illustrating the need to understand the context of a conserved signaling pathway in tailoring patient treatments.


- 2675** CK2 α' Drives Lung Cancer Metastasis by Targeting BRMS1 Nuclear Export and Degradation
Yuan Liu, Elianna B. Amin, Marty W. Mayo, Neel P. Chudgar, Peter R. Bucciarelli, Kyuichi Kadota, Prasad S. Adusumilli, and David R. Jones
Précis: This study identifies an actionable posttranslational regulatory mechanism that blocks metastasis, including possibly in heterogeneous cellular states that are inherent to this advanced disease state.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 2687** CRM1 Inhibition Promotes Cytotoxicity in Ewing Sarcoma Cells by Repressing EWS-FLI1-Dependent IGF-1 Signaling
Haibo Sun, De-Chen Lin, Qi Cao, Xiao Guo, Helene Marijon, Zhiqiang Zhao, Sigal Gery, Liang Xu, Henry Yang, Brendan Pang, Victor Kwan Min Lee, Huey Jin Lim, Ngan Doan, Jonathan W. Said, Peiguo Chu, Anand Mayakonda, Tom Thomas, Charles Forscher, Erkan Baloglu, Sharon Shacham, Raja Rajalingam, and H. Phillip Koeffler
Précis: These findings provide a strong rationale to investigate the combinatorial efficacy of an inhibitor of nuclear export and the IGF-1 receptor to treat the aggressive soft tissue tumor Ewing sarcoma.
- 2698** Natural Product Vibsanin A Induces Differentiation of Myeloid Leukemia Cells through PKC Activation
Zu-Yin Yu, He Xiao, Li-Mei Wang, Xing Shen, Yu Jing, Lin Wang, Wen-Feng Sun, Yan-Feng Zhang, Yu Cui, Ya-Jun Shan, Wen-Bing Zhou, Shuang Xing, Guo-Lin Xiong, Xiao-Lan Liu, Bo Dong, Jian-Nan Feng, Li-Sheng Wang, Qing-Liang Luo, Qin-Shi Zhao, and Yu-Wen Cong
Précis: A plant-derived factor with potent antileukemia activity may serve as a novel differentiation-inducing agent to treat acute myeloid leukemias that do not respond to all-trans retinoic therapy, a present standard of care.

- 2710** Intracellular Released Payload Influences Potency and Bystander-Killing Effects of Antibody-Drug Conjugates in Preclinical Models
 Fu Li, Kim K. Emmerton, Mechthild Jonas, Xinqun Zhang, Jamie B. Miyamoto, Jocelyn R. Setter, Nicole D. Nicholas, Nicole M. Okeley, Robert P. Lyon, Dennis R. Benjamin, and Che-Leung Law
Précis: These findings suggest that the antitumor activity of antibody-drug conjugates appears to depend primarily on the amount and property of the drug payload released at the target site, with general implications for developing this class of cancer drugs.

- 2720** HSP70 Inhibition Limits FAK-Dependent Invasion and Enhances the Response to Melanoma Treatment with BRAF Inhibitors
Anna Budina-Kolomets, Marie R. Webster, Julia I-Ju Leu, Matthew Jennis, Clemens Krepler, Anastasia Guerrini, Andrew V. Kossenkov, Wei Xu, Giorgos Karakousis, Lynn Schuchter, Ravi K. Amaravadi, Hong Wu, Xiangfan Yin, Qin Liu, Yiling Lu, Gordon B. Mills, Xiaowei Xu, Donna L. George, Ashani T. Weeraratna, and Maureen E. Murphy
Précis: These findings provide strong support for HSP70 inhibition as a therapeutic strategy in melanoma, especially as an adjuvant approach for overcoming the resistance to BRAF inhibitors frequently observed in melanoma patients.

- 2731** Second-Generation HSP90 Inhibitor Onalespib Blocks mRNA Splicing of Androgen Receptor Variant 7 in Prostate Cancer Cells
 Roberta Ferraldeschi, Jonathan Welti, Marissa V. Powers, Wei Yuan, Tomoko Smyth, George Seed, Ruth Riisnaes, Somaieh Hedayat, Hannah Wang, Mateus Crespo, Daniel Nava Rodrigues, Ines Figueiredo, Susana Miranda, Suzanne Carreira, John F. Lyons, Sweet Sharp, Stephen R. Plymate, Gerhard Attard, Nicola Wallis, Paul Workman, and Johann S. de Bono
Précis: A novel mechanism of action for HSP90 inhibitors involving the suppression of androgen receptor splicing strengthens predictions that these therapeutics may elicit potent clinical responses in advanced prostate cancers.

- 2743** GSK-3 Inhibition Sensitizes Acute Myeloid Leukemia Cells to 1,25D-Mediated Differentiation
Kalpana Gupta, Tammy Stefan, James Ignatz-Hoover, Stephen Moreton, Gary Parizher, Yogen Saunthararajah, and David N. Wald
Précis: These findings offer a preclinical rationale to reposition GSK3 inhibitors in clinic to enhance a novel differentiation-based therapy for AML treatment.

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2754 Stress Chaperone Mortalin Contributes to Epithelial-to-Mesenchymal Transition and Cancer Metastasis

Youjin Na, Sunil C. Kaul, Jihoon Ryu, Jung-Sun Lee, Hyo Min Ahn, Zeenia Kaul, Rajkumar S. Kalra, Ling Li, Nashi Widodo, Chae-Ok Yun, and Renu Wadhwa

Précis: These findings suggest that the aberrant enrichment of a stress chaperone protein in multiple tumor types elicits an EMT-like phenotype and promotes the invasiveness of cancer cells, warranting further investigation as a potentially broad-acting therapeutic target.

2766 Quantitative Phosphotyrosine Profiling of Patient-Derived Xenografts Identifies Therapeutic Targets in Pediatric Leukemia

Sibasish Dolai, Keith C.S. Sia, Alissa K. Robbins, Ling Zhong, Sue L. Heatley, Tiffany L. Vincent, Falko Hochgräfe, Rosemary Sutton, Raushan T. Kurmasheva, Tamas Revesz, Deborah L. White, Peter J. Houghton, Malcolm A. Smith, David T. Teachey, Roger J. Daly, Mark J. Raftery, and Richard B. Lock

Précis: Phosphotyrosine profiling of patient-derived xenografts may offer an unbiased quantitative approach to define aberrant signaling nodes and identify clinically actionable targets in pediatric leukemias.

2778 The BRCA1- Δ 11q Alternative Splice Isoform Bypasses Germline Mutations and Promotes Therapeutic Resistance to PARP Inhibition and Cisplatin

Yifan Wang, Andrea J. Bernhardt, Cristina Cruz, John J. Kraus, Joseph Nacson, Emmanuelle Nicolas, Suraj Peri, Hanneke van der Gulden, Ingrid van der Heijden, Shane W. O'Brien, Yong Zhang, Maribel I. Harrell, Shawn F. Johnson, Francisco J. Candido Dos Reis, Paul D. P. Pharoah, Beth Karlan, Charlie Gourley, Diether Lambrechts, Georgia Chenevix-Trench, Håkan Olsson, Javier J. Benitez, Mark H. Greene, Martin Gore, Robert Nussbaum, Siegal Sadetzki, Simon A. Gayther, Susanne K. Kjaer, kConFab Investigators, Alan D. D'Andrea, Geoffrey I. Shapiro, David L. Wiest, Denise C. Connolly, Mary B. Daly, Elizabeth M. Swisher, Peter Bouwman, Jos Jonkers, Judith Balmaña, Violeta Serra, and Neil Johnson

Précis: Cancer cells generate BRCA splice isoforms to evade the deleterious effects of germline mutations, producing altered proteins capable of promoting therapeutic resistance and thereby targets for resensitization.

TUMOR AND STEM CELL BIOLOGY

2791 Heparanase 2 Attenuates Head and Neck Tumor Vascularity and Growth

Miriam Gross-Cohen, Sari Feld, Ilana Doweck, Gera Neufeld, Peleg Hasson, Gil Arvatz, Uri Barash, Inna Naroditsky, Neta Ilan, and Israel Vlodavsky

Précis: These findings show how overexpression of an isoform of heparanase, Hpa2, inhibits the malignant growth of head and neck cancers, which are rising in incidence.

2802 JPO2/CDCA7L and LEDGF/p75 Are Novel Mediators of PI3K/AKT Signaling and Aggressive Phenotypes in Medulloblastoma

Tiffany Sin Yu Chan, Cynthia Hawkins, Jonathan R. Krieger, C. Jane McClade, and Annie Huang

Précis: Studies identify a novel complex interacting with Myc and Akt kinase as a critical mediator of metastatic behavior in medulloblastoma, with potential implications as a novel point for therapeutic intervention in this type of brain cancer.

2813 MIF Maintains the Tumorigenic Capacity of Brain Tumor-Initiating Cells by Directly Inhibiting p53

Raita Fukaya, Shigeki Ohta, Tomonori Yaguchi, Yumi Matsuzaki, Eiji Sugihara, Hideyuki Okano, Hideyuki Saya, Yutaka Kawakami, Takeshi Kawase, Kazunari Yoshida, and Masahiro Toda

Précis: These findings suggest that a macrophage-secreted factor regulates the formation of tumor-initiating cells in brain cancer by directing binding p53, shedding light on how these important drivers of malignancy are formed.

2824 Analysis of Liver Tumor-Prone Mouse Models of the Hippo Kinase Scaffold Proteins RASSF1A and SAV1

Xiaoying Zhang, Cai Guo, Xiwei Wu, Arthur X. Li, Limin Liu, Walter Tsark, Reinhard Dammann, Hui Shen, Steven L. Vonderfecht, and Gerd P. Pfeifer

Précis: Liver tumor susceptibility of mouse models in which the Hippo kinase scaffold proteins RASSF1A and SAV1 were deleted suggest a more prominent role of SAV1 as a tumor suppressor in the mouse, which cannot easily be extrapolated to human HCC.

2836 Bap1 Is a Bona Fide Tumor Suppressor: Genetic Evidence from Mouse Models Carrying Heterozygous Germline Bap1 Mutations

Yuwaraj Kadariya, Mitchell Cheung, Jinfei Xu, Jianming Pei, Eleonora Sementino, Craig W. Menges, Kathy Q. Cai, Frank J. Rauscher, Andres J. Klein-Szanto, and Joseph R. Testa

Précis: Studies in mouse genetic models offer proof of concept for the suggested tumor suppressor function for BAP1, a gene that when mutated, confers a risk of several tumors, including asbestos-induced mesothelioma.



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CORRECTIONS

2845 Correction: Grapefruit-Derived Nanovectors Use an Activated Leukocyte Trafficking Pathway to Deliver Therapeutic Agents to Inflammatory Tumor Sites

2846 Correction: Radiation-Induced Loss of Salivary Gland Function Is Driven by Cellular Senescence and Prevented by IL6 Modulation

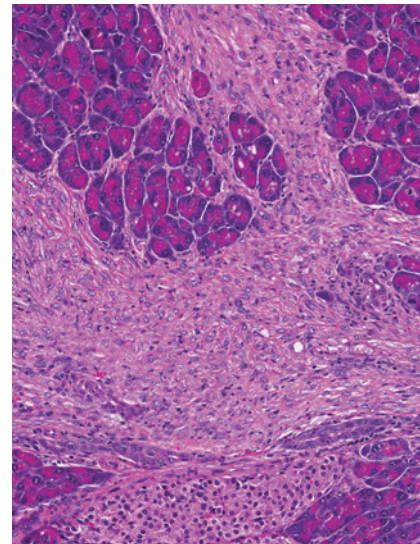
2847 Correction: Aberrant Notch Signaling in the Bone Marrow Microenvironment of Acute Lymphoid Leukemia Suppresses Osteoblast-Mediated Support of Hematopoietic Niche Function

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ABOUT THE COVER

Individuals harboring inherited heterozygous mutations of the *BAP1* gene are predisposed to a spectrum of neoplasms, including malignant mesothelioma. Using genetically engineered mouse models, it was found that inactivating germline *Bap1* mutations behave as potent cancer susceptibility alleles, giving rise to a variety of malignant tumor types, including occasional mesotheliomas. However, high penetrance of mesothelioma in *Bap1*-mutant mice required exposure to asbestos. The image depicts hematoxylin and eosin staining of a spontaneous malignant mesothelioma invading the pancreas of mouse with a germline *Bap1* mutation. For details, see article by Kadariya and colleagues on page 2836.



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